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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,844	SCHWINN, DEBRA A.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,27-30 and 33-37* is/are pending in the application.

4a) Of the above claim(s) *27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,29,30 and 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed October 22, 2007. Currently, claims 25, 27-30, 33-37 are pending. Claims 27-28 have been withdrawn as drawn to non-elected subject matter.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 22, 2007 has been entered.

3. This Office action has an attached requirement for information under 37 CFR 1.105. A complete reply to this Office action must include a complete reply to the attached requirement for information. The time period for reply to the attached requirement coincides with the time period for reply to this Office action.

Election/Restrictions

4. Applicant's election with traverse of Group I, Claims 1-7 in the paper filed January 17, 2006 is acknowledged.

The response asserts that there would be no burden to search the entire application. This argument has been thoroughly reviewed, but not found persuasive because each of the groups are separately classified which provides a prima facie

support for burden. For all of the reasons previously presented, the methods and products are distinct.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims drawn to an invention nonelected with traverse in the paper filed January 17, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Newly submitted claims 27-28 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Each DNA polymorphisms is patentably distinct. A search for G247R is not coextensive of a search for V311I. Each polymorphism is not obvious over any other polymorphism. The original claims encompassed the single polymorphism of G247R which was treated on the merits. In the event a generic claim becomes allowable, applicant would be entitled to the species encompassed by the claims.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 27-28, 32 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Priority

5. This application claims priority to provisional application 60/427,219, filed November 19, 2002.

Requirement for Information

6. Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

The following Meeting Abstract from the Third International SNP meeting September 8-11, 2000 is reproduced below.

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NOVEL Alpha1a-ADRENERGIC RECEPTOR (Alpha1aAR) SNPs AND HUMAN HYPERTENSION

DEBRA SCHWINN, Steve Beckstrom-Sternberg, and Eric Green
Duke University Medical Center, National Human Genome Research Institute, and NIH Intramural Sequencing Center

Sympathetically-mediated vasoconstriction is known to be an important etiologic factor in hypertension. Due to mammalian tissue heterogeneity in alphaAR subtype expression, it is important to study human DNA to understand sympathetically-mediated hypertension. Recent identification by our laboratory of the alpha1aAR subtype in human splanchnic and resistance vessels(1), in conjunction with previous linkage of human chromosome 8p21–p22 with hypertension (2), led to our hypothesis that alpha1aAR-specific SNPs may be associated with hypertension. We are employing a systematic sequencing strategy to identify SNPs in the alpha1aAR gene and its flanking DNA. Specifically, we are sequencing 5 kb of genomic DNA (2.2 kb encompassing a1aAR and 3 known splice variants, 2.8 kb of 5′ regulatory and 5′ UTR sequence) in large sets of individuals. This involves PCR amplification of 18 amplimers (400–500 bp each), direct sequencing of PCR products, and the use of PolyPhred (3) to identify SNPs. DNA has already been obtained from 280 individuals (90 random individuals within the Coriell panel and 190 well-phenotyped patients representing 3 distinct types of hypertension, selected at the extremes of blood pressure). Although early in the analyses, we have already identified 1 known and >8 novel SNPs within Coriell panel individuals (found in coding sequence, splice variant regions, and 5′–regulatory sequence). Allele frequencies range from 0.01 (confirmed) to 0.48; some of the SNPs identified reflect base changes that result in non-conservative substitutions in the coding region. Data from patients with and without hypertension are currently being sequenced and will be presented.

1. Rudner XL, et al, Circulation, 1999, 100: 2336–43.
2. Wu DA, et al, J Clin Invest, 1996, 97: 2111–8.
3. http://droog.mbt.washington.edu/PolyPhred.html

Applicants are requested to provide the following information.

1. Did applicant or assignee, or a representative thereof, present the information provided in the above abstract. If so, applicants are requested to indicate the date of the presentation, and the location of the presentation.

2. In view of the statements that data from patients with and without hypertension will be presented, applicants are required to provide any slides, posters, or handouts that were provided at the meeting which any of the applicants authored or co-

authored or which describe the disclosed subject matter referred to in the abstract. Applicants are further requested to provide the data from the patients with and without hypertension which was presented.

3. Is the applicant or assignee aware of any other presentations or publications of their data related to patients with and without hypertension and Alpha1aAR. If so, applicants are requested to provide the location of the presentation or publication and any slides, posters, or handouts prepared.

The fee and certification requirements of 37 CFR 1.97 are waived for those documents submitted in reply to this requirement. This waiver extends only to those documents within the scope of this requirement under 37 CFR 1.105 that are included in the applicant's first complete communication responding to this requirement. Any supplemental replies subsequent to the first communication responding to this requirement and any information disclosures beyond the scope of this requirement under 37 CFR 1.105 are subject to the fee and certification requirements of 37 CFR 1.97.

The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

This requirement is an attachment of the enclosed Office action. A complete reply to the enclosed Office action must include a complete reply to this requirement. The time period for reply to this requirement coincides with the time period for reply to the enclosed Office action.

This Office action has an attached requirement for information under 37 CFR 1.105. A complete reply to this Office action must include a complete reply to the attached requirement for information. The time period for reply to the attached requirement coincides with the time period for reply to this Office action.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 25, 29-30, 33-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from

its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The pending claims encompass a large genus of nucleic acids which comprise polymorphisms in the TM4, TM5 or TM7 or IL3 regions of alpha1A adrenergic receptor gene. The claims encompass a large number of polymorphisms and mutations for which no written description is provided in the specification. As provided in Example 11, no common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus of alterations in alpha1A adrenergic receptor is highly variant, the specific mutations taught alone are insufficient to describe the genus. There is no description of the mutational sites that exist in nature and there is no description of how

the structure of alpha1A adrenergic receptor relates to the structure of any strictly neutral alleles.

The alterations to be detected by methods of the invention are nucleic acid mutations including a point mutation that results in an amino acid substitution in a transmembrane helix selected from the TM4, TM5 and TM7 or the IL3. The specification fails to provide any description as to which nucleic acid changes which cause amino acid changes are associated with disease.

The general knowledge in the art concerning variants does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only 5 member of this genus is not representative of the variants of the genus and is insufficient to support the claim. The TM4, TM5, TM7 and IL3 encompass a region of more than 100 amino acids.

The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms with any disease. The polymorphisms shown are not representative of the genus of any polymorphism associated with diseases because it is not clear which, if any, polymorphisms in alpha1A adrenergic receptor would have the same affect.

Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Response to Arguments

The response traverses the rejection. The response asserts that the claims encompass point mutations that result in an amino acid substitution in a specified region of the alpha1aAR gene. This argument has been considered but is not convincing because the claim remains drawn to a large genus of point mutations that may result in amino acid substitutions in the recited regions, however the specification fails to provide a representative number of mutations which change the amino acid and which are associated with disease. While the specification and the post filing date art illustrates 4 mutations in the recited region alter activity, the association of these point mutations have not been described as disease mutations as required by the instant claims17. Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112-- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 25, 29-30, 33-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 25, 29-30, 33-37 are drawn to a method of detecting disease, including cardiovascular disease, cancer or a psychiatric disease, in a patient by screening DNA present in the sample for at least on mutation in alpha1A adrenergic receptor gene.

The nature of the invention, therefore, requires the knowledge of predictive associations between any alteration in any alpha1A adrenergic receptor gene nucleic acid for any subject and diagnosis of any disease.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches the lack of association between mutations in the alpha1A Adrenergic receptor and diseases.

Xie (Pharmacogenetics, Vol. 9, pages 651-656, 1999) teaches the adrenergic receptor polymoprhism is not associated with essential hypertension. Xie clearly states

that the Arg492Cys (Arg347Cys) polymorphism is not associated with essential hypertension in black or white Americans (abstract).

Bolonna et al. (Neuroscience Letters, Vol. 280, pages 65-68, 2000) teaches no influence of adrenergic receptor polymorphisms on schizophrenia and antipsychotic response. Analysis of the Arg492Cys polymorphism in alpha1A Adrenergic receptor did not show a clear difference between the different groups suggesting that the polymorphism did not play an important role in the etiology of the disorder or in determining antipsychotic response (abstract, Table 1).

Forleo et al. (JACC, page 274A, March 19, 2003) teaches no significant differences were found between alpha1A Adrenergic receptor polymorphisms and non-sustained ventricular tachycardia or altered baroflex sensitivity.

Sofowora et al. (Clin.. Pharmacol. Ther. Vol. 75, pages 539-545, 2004) teaches alpha1A Adrenergic receptor polymorphism and vascular response. The Arg 347Cys polymorphism does not alter agonist-mediated venoconstriction in vivo (abstract). Sofowora states that although our study indicates that the Arg347Cys alpha1A Adrenergic receptor polymorphism is not responsible for differences in phenylephrine responsiveness, other possible polymorphisms may exist, suggesting further experimentation is required (page 543, col. 2). Specifically Sofowora teaches that further study is required to identify other polymorphisms in the alpha1A Adrenergic receptor (page 543, col. 2).

Clark et al. (Biol. Psychiatry, Vol. 58, pages 435-439, 2005) teaches polymorphisms in the promoter region of the alpha1A Adrenergic receptor and association with schizophrenia. Analysis of 8 SNPs was performed and association was found for the –563 SNP and –9625 SNP, however the other 6 polymorphisms did

not show an association. Thus, it is unpredictable which polymorphisms are and which polymorphisms are not associated with schizophrenia.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7

has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification provides no evidence that any mutation or alteration in the alpha1A Adrenergic receptor is associated with a disease, including a cardiovascular diseases, a psychiatric disease or cancer.

The specification teaches SNPS at nucleotides 460, 497, 599, 739, 931, 1039, 1395 of the human alpha1A Adrenergic receptor.

The specification teaches the frequency of each of the polymorphisms in various populations including black, Hispanic and Caucasian groups. The Mutation at 247 is not present in black or Caucasian individuals. Hispanic individuals are the only individuals which appear to exhibit the polymorphism. Thus, detecting disease using the polymorphism in black and Caucasian individuals would be unpredictable.

The specification does not specifically analyze the presence of any of the polymorphisms with any of the diseases.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied

The specification teaches only 5 specific polymorphisms in relation to the protein amino acid position which are within the scope of the instant claims. No common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphisms with any diseases is provided. The specification fails to provide a predictable correlation with the alterations and any disease. As provided by the art, genetic association studies are unpredictable, even within the same gene which shows association with a disease (see Meyer). The prior art and the post filing date art specifically teach polymorphisms within the alpha1A Adrenergic receptor gene which are not associated with particular diseases. For example, Bolonna teaches an analysis of the Arg492Cys polymorphism in alpha1A Adrenergic receptor did not show a clear difference between the different groups suggesting that the polymorphism did not play an important role in the aetiology of the disorder or in determining antipsychotic response (abstract, Table 1). Moreover, Xie teaches Arg492Cys is not associated with essential hypertension in either black or white Americans. Therefore, it is clear that it is unpredictable whether particular polymorphisms in the alpha1A Adrenergic receptor gene are associated with a disease, including a psychiatric disease.

The specification provides no evidence that any SNP at such position provides a predictable association with a disease, including psychiatric disease or cancer. The quantity of experimentation in this area is extremely large as it requires analysis of each position in the alpha1A Adrenergic receptor gene to determine whether any alteration at each position is associated with a disease, with the outcome of each analysis being

unpredictable. While one could conduct additional experimentation to determine whether, e.g. other positions in the alpha1A Adrenergic receptor gene might be associated with a disease in any other patient, the outcome of such research cannot be predicted and such further research and experimentation is both unpredictable and undue. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the unpredictability of polymorphism association studies, the instant claims are not enabled over the broad scope. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that none of the references cited by the Examiner relate to point mutations that result in amino acid changes in the regions of the receptor recited in the claims as now presented. This argument has been considered and is correct. However, the references directed to other polymorphisms in the same gene illustrates the unpredictability of SNPs regardless of their region in the gene. The art provides significant teachings regarding the unpredictability of mutation associations. Furthermore, the response does not appear to address the unpredictability of various SNPs.

The response asserts that the reliance on Meyer is not understood. Meyers was relied upon to demonstrate that the state of the art was such that polymorphisms within the same gene are not similarly associated with diseases. Meyers illustrates one polymorphism is associated with a disease, whereas another polymorphism is relatively close proximity is not similarly associated with the disease.

Moreover, Hirschhorn and Ioannidis demonstrate the state of the art regarding association studies. The state of the art is such that association studies are not reliably associated and are often unreplicatable.

The response asserts that residue 347 is not within the C-terminus. This argument does not appear to be supported by Table 6. Table 6 illustrates that the domain is the C-terminus.

The response asserts that *meaningful conclusions as to associations between mutations and diseases must be based on samples of such size as to enable appropriate statistical analysis.* The examiner fully agrees with this assertion. However,

in the instant specification there are no association studies, of any size or any statistical significance. The specification fails to take a population of diseased patients, and a population of controls to analyze the frequencies of particular point mutations, as required by the instant claims. Thus, while the examiner agrees with applicant's position, there does not appear to be any association studies provided within the scope of the instant claims to support a meaningful conclusion.

The response asserts that pages 21-25 of the specification analyze polymorphisms with disease. This argument has been thoroughly reviewed but is not persuasive. A review of the specification fails to provide any populations of individuals with any disease, let alone a representative number of diseases to enable the broad scope of the claims. Page 20 is entitled the effects of human alpah1aAR SNP G247R on surface receptor expression and norephinephrine-mediated internalization, effects of human alpah1aAR SNPs on cell growth, for example. These effects do not provide any guidance as to how the point mutations are associated with any disease, or more specifically hypertension, for example. With respect to the predictive nature of the text on page 25, the instant specification fails to provide any guidance as to a reliable association between the polymorphisms and any disorder. As noted in the response, "meaningful conclusions as to associations between mutations and diseases must be based on samples of such size as to enable appropriate statistical analysis." Here, there are no such samples and no such statistical analysis. Thus, trial and error experimentation would be required to determine whether the polymorphisms are associated with diseases generally and any disease in particular.

Thus for the reasons above and those already of record, the rejection is maintained.

New Matter

9. Claims 25, 29, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "an amino acid substitution in a transmembrane helix selected from TM4, TM5 and Tm7" or "in the third intracellular loop" are included. The amendment does not point to support in the instant specification for the generic teachings of a transmembrane helix or an intracellular loop. However, the specification does not broadly describe or discuss "an amino acid substitution in a transmembrane helix selected from TM4, TM5 and Tm7" or "in the third intracellular loop". Instead the specification teaches particular SNPs in the TM4, TM5 TM7 and IL3. This description does not support "an amino acid substitution in a transmembrane helix selected from TM4, TM5 and Tm7" or "in the third intracellular loop". The concept of "an amino acid substitution in a transmembrane helix selected from TM4, TM5 and Tm7" or "in the third intracellular loop" does not appear to be part of the originally filed invention. Therefore, "an amino acid substitution in a transmembrane helix selected from TM4, TM5 and Tm7" or "in the third intracellular loop" constitutes new matter.

Response to Arguments

The response traverses the rejection. The response asserts there is no basis for the rejection of Claims 25, 29-30, 33-37. This argument has been considered but is not

convincing. The response pointed to Figure 2 which illustrates the transmembrane helix and loops, but does not contemplate any mutations within these smaller ranges. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

10. No claims allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
January 7, 2008

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER